October 26, 2009
FDA Anti-Infective Drugs Advisory Committee Meeting

Clinical and Laboratory Standards Institute (CLSI)

Glen Fine
Executive Vice President

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Agenda

- CLSI Background
  - CLSI's role in international & US standards development
- How does CLSI work?
  - The CLSI consensus process
- CLSI & Antimicrobial Susceptibility Testing (AST)
  - CLSI has 30+ years experience creating MIC standards

CLSI Background

- CLSI is:
  - A non-profit organization
    - IRS 501c3 (educational mission)
    - Founded 41 years ago as NCCLS
  - An accredited standards development organization
    - American National Standards Institute (ANSI)
  - Closely linked to the International Organization for Standardization (ISO)

CLSI & ISO

- International Organization for Standardization (ISO) is
  - The world's largest developer of international standards
  - A network of the national standards institutes of 162 countries, one member per country
- CLSI is the Executive Secretariat for
  - The ISO Committee for the Clinical Laboratory
  - The ISO Subcommittee on Anti-microbial Susceptibility Testing
- CLSI's antibacterial MIC method & QC values
  - Are the basis of 2 ISO standards

CLSI & WHO

- World Health Organization (WHO)
  - The directing and coordinating authority for health within the United Nations system
  - Responsible for providing leadership on global health matters, **setting norms and standards**, and providing technical support to countries and monitoring and assessing health trends
- CLSI is
  - The only WHO-designated collaborating center for clinical laboratory standards in the world

Use of Standards is Encouraged

- Using voluntary consensus standards is
  - Efficient
  - Cost-effective
  - Encouraged by a variety of policies
- Example: US Government OMB Circular A-119
  - Establishes policies for federal use and development of voluntary consensus standards
  - Directs agencies to use such guidelines in lieu of government-unique standards unless impractical
  - Defines the characteristics of a good voluntary consensus organization

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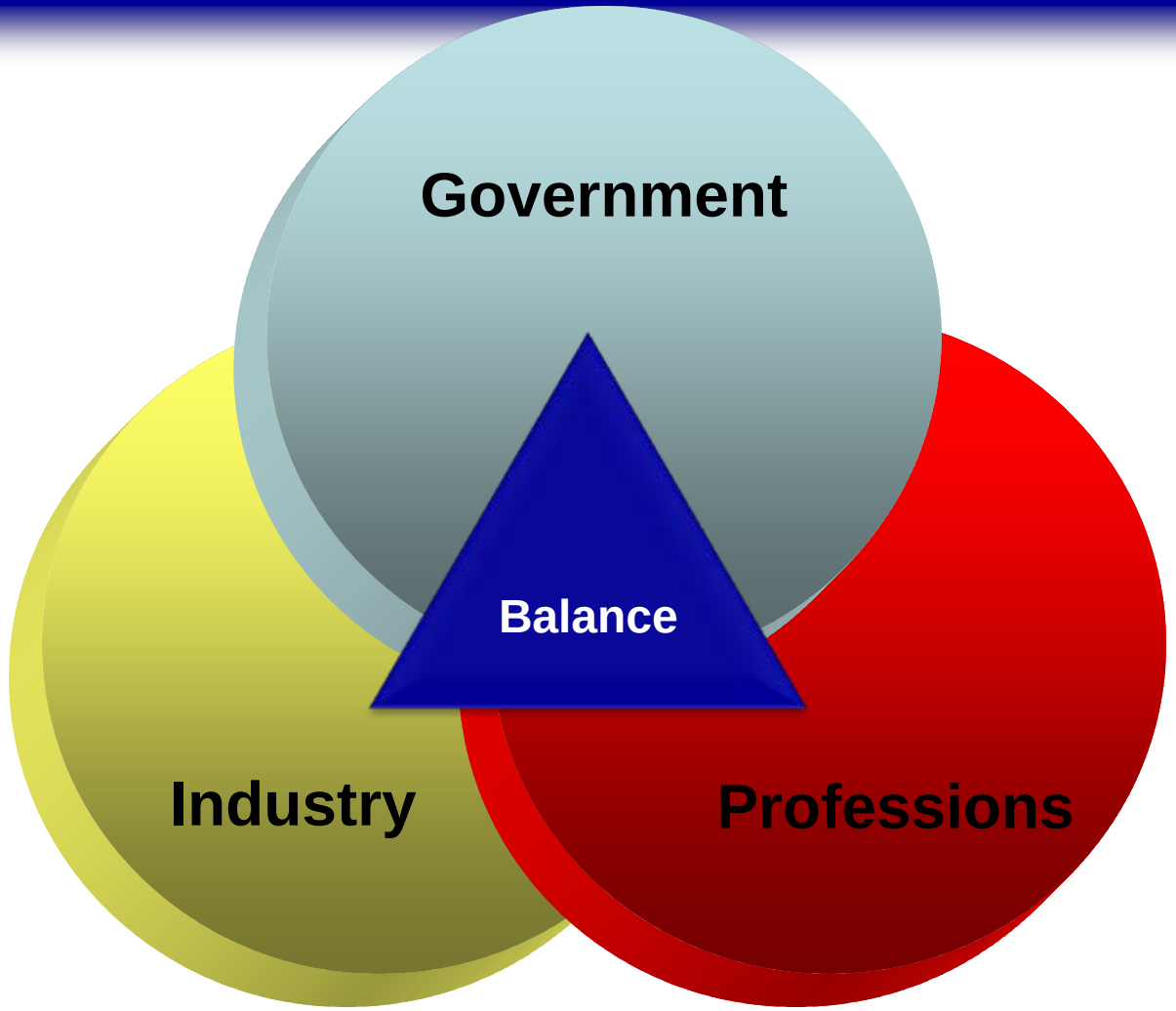
CLSI's Member Organizations

- Public & Private Labs, Industry & Government
  - 1,600 hospitals and laboratories
  - 130 industry organizations
  - 40 government agencies
  - 40 startup companies & consultants
- Institutions & Societies
  - 70 educational institutions
  - 35 professional societies
- Member organizations represent 70+ countries

Volunteers

- > 2,000 volunteers write CLSI's library of >200 standards & guidelines
- >75 active projects ongoing at any given time
- Volunteers are scientific thought leaders and well respected in their field
  - Most hold a PhD or an MD
- CLSI volunteers have global reach
  - Approximately 30% reside outside North America

CLSI Consensus Process



CLSI's Consensus Process

- Fully Open Process: Meetings available to all
- Transparent: Materials are fully available
- Inclusive: Industry, Academia & Government
- Balance of Interests
- Conflict of Interests Fully Disclosed
- Appeals Process

Agenda

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CLSI & Antimicrobial Susceptibility Testing (AST)

- CLSI has been the World Leader for 30+ years in:
  - Establishing the Methods for AST Testing
  - Establishing Quality Control ranges
  - Establishing & maintaining updated Interpretive Breakpoints
- The CLSI AST Committees are
  - Comprised of world-renowned experts
  - Includes representatives from Academic, Infectious Disease, Regulatory and Public health agencies, EUCAST and EMEA, etc.

CLSI & Antimicrobial Susceptibility Testing (AST)

- ANSI has approved CLSI's AST standards as US National Standards
- National lab accrediting bodies (CLIA…CAP) require methods consistent with CLSI standards
- CLSI methods and interpretive criteria are used in almost every US clinical microbiology laboratory
- CLSI AST standards are de facto national standards in over 50 countries, and translated into six languages

CLSI & Antimicrobial Susceptibility Testing (AST)

- For over 2 decades, CLSI AST interpretive criteria have been embedded in the software of the FDA-cleared devices producing >85% of all microbial identifications and susceptibility testing results.
- FDA-approved drug labels reference CLSI/NCCLS testing methods and QC measures as being the relevant national standards
- FDA CDRH requires that CLSI methods be used as the reference procedures to which any new device is compared for FDA clearance

CLSI & Antimicrobial Susceptibility Testing (AST)

- CLSI's Microbiology Standard Methods include
  - M23: Developing Interpretive Criteria & QC parameters
  - M2 & M7: Broth & agar-based testing of aerobic bacteria
  - M11: Testing of anaerobic bacteria
  - … and 32 others
- These method documents are updated regularly
  - Semiannual face-to-face meetings
  - Teleconferences
  - Subcommittees and Working groups
- All material & processes are open for review

Conclusion

- As an active participant in international standards development, CLSI welcomes the FDA's plan to use recognized public voluntary consensus standards
- CLSI is a well established and highly respected leader in the development of such standards
  - All CLSI methods are updated regularly using best current knowledge from world-renowned experts
  - All CLSI interpretive breakpoints are current, reviewed annually, and updated as needed to address emerging bacterial resistance and new methodological insights

Conclusion

- CLSI has had longstanding participation from the FDA
  - FDA representatives participate in all major subcommittees
- CLSI looks forward to enhancing its already excellent relationship with the FDA in implementing updated Microbiology Data in Systemic Antibacterial Drug Products

INFECTIOUS DISEASES SOCIETY OF AMERICA'S (IDSA)
STATEMENT CONCERNING UPDATING SUSCEPTIBILITY TEST INFORMATION
IN SYSTEMIC BACTERIAL DRUG PRODUCT LABELING
October 26, 2009

Good morning. I am Robert J. Guidos, JD, Vice President of Public Policy and Government Relations for the Infectious Diseases Society of America (IDSA). On behalf of IDSA's membership, comprised of more than 9,000 infectious diseases physicians and scientists, I want to thank the U.S. Food and Drug Administration (FDA) for the invitation to present here today on the topic of updating susceptibility test information in systemic antibacterial drug product labeling. IDSA welcomes the opportunity to discuss the history and past processes employed to update susceptibility interpretative criteria ("breakpoints"); how best to expedite future updates of antibacterial drug labels and antimicrobial susceptibility testing (AST) devices' algorithms (90% of U.S. microbiology laboratories use these devices) as new evidence and recommendations concerning breakpoints are made available; and how best to expedite updating the breakpoint information on the approximately seventy (70) out-of-date antibacterial drug labels that FDA's internal review has uncovered.

As members of the Anti-Infective Drugs Advisory Committee (AIDAC) already know, physicians need accurate information on breakpoints to use antibacterial drugs wisely. Break-points are the science behind standard laboratory policy and are the basis upon which antibacterial drug selection determinations are made. The real-life impact of relying upon inaccurate (including out-of-date) breakpoints are thousands of wrong treatment decisions being made every day in this country. Without accurate breakpoint information, patients' safety and lives are at risk. That is why updating antibacterial drug product labeling and AST instruments/systems in a timely manner are so critically important. It is IDSA's position that breakpoints should be reviewed and updated on a regular basis as clinical need dictates and that this should occur at least every few years.

IDSA experts have identified several recent examples where breakpoints need to be updated quickly. These include the Clinical Laboratory Standards Institute's[1] (CLSI) June 2009 recommendations to: (1) lower breakpoints for extended spectrum cephalosporins versus *Enterobacteriaceae* for better detection of ESBL-producing enteric gram-negative bacilli, and (2) lower breakpoints for carbapenems versus *Enterobacteriaceae* for better detection of carbapenemase-producing enteric gram-negative resistant organisms, such as *K. pneumoniae.*

It must be noted that prior to 2006, an FDA Center for Devices and Radiological Health (CDRH) guidance allowed AST device manufacturers to include in their devices' algorithms both FDA-established breakpoints listed in package inserts at the time of the drug's approval as well as the more up-to-date breakpoint recommended by CLSI. In 2006, in what can best be described as an attempt at regulatory perfection, FDA withdrew its AST device guidance document, a workable process employed for decades, and began to require CLSI to submit citizen petitions to the

[1] CLSI is a 501(c)(3) nonprofit organization, comprised of experts in infectious diseases and clinical microbiology. CLSI is not affiliated with IDSA.

agency when recommending updated breakpoints. In IDSA's estimation, the citizens' petition process was a non-starter due to the time delays it created. Regarding updating antibacterial drug labels, as FDA's briefing document makes clear, the Center for Drug Evaluation and Review (CDER) has done a very poor job in this regard over the last several decades, which is why CLSI stepped in. With this history in mind, in 2006-2007, IDSA lobbied the U.S. Congress to require FDA to establish workable processes for expeditiously updating antibacterial breakpoints. As noted in FDA's briefing document, Congress agreed to this request and included provisions in the FDA Amendments Act of 2007 to require FDA to identify and periodically update breakpoints. In response, FDA published its June 2009 Guidance for Industry: Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices. IDSA applauds FDA's decision to allow the agency to consider and adopt breakpoints established by nationally and internationally recognized standard setting organizations, like CLSI. However, it is evident from the outset that the new guidance is unusable, unless processes can be established to allow for expedited adoption of nationally and internationally recognized standard setting organizations' recommendations.

FDA's Office of Antimicrobial Products' briefing document does a nice job of laying out the background, issues, and likely problems that are going to arise under FDA's new guidance. Most notable is FDA's comment that the process would take "some time" to complete. In IDSA's estimation, updating breakpoint information under the guidance could easily take two to three years, placing patients' lives and safety at risk in the interim.

For that reason, IDSA calls upon AIDAC members to recommend that FDA adopt the most streamlined, expeditious approaches possible for updating drug labeling and device algorithms with breakpoint information.

- IDSA's preference is that the agency allow for immediate adoption of newly recommended nationally and internationally recognized standard setting organizations' standards on both drug labeling and AST devices once those standards have been published in the National Library of Medicine or Library of Congress, as FDA's June 2009 guidance requires. These standards then could be allowed on labeling and in algorithms along with the existing FDA-established breakpoints, until such time as FDA makes a final determination that the nationally and internationally recognized standard setting organization's standard alone is appropriate.

- In combination with the immediate adoption approach just mentioned or, as an alternative to that approach (IDSA's second choice), IDSA recommends that FDA modify the "practical application" outlined on Page 7 of its briefing document to move earlier in the process the new drug application (NDA) holders' review and feedback step. That is, immediately following the publishing of a nationally and internationally recognized standard setting organization's standard in the National Library of Medicine or Library of Congress, FDA itself should publish in the Federal Register a notice of the nationally and internationally recognized standard setting organization's posting and call for NDA holders of relevant systemic antibacterial drugs to evaluate their product labeling in

relation to the nationally and internationally recognized standard setting organization's recommended new standard and then take one of following three steps within 60 days:

1) submit labeling in conformance with the nationally and internationally recognized standard setting organization's recommended new standard;
2) submit scientific data supporting why a different change to their product labeling is more appropriate; or
3) submit a scientific justification demonstrating why no change is needed if the microbiology information for the antibacterial drug product differs from the recommended new standard.

Moving this step earlier will save significant time as FDA can then consider information submitted by the NDA holder(s) at the same time it is considering the new nationally and internationally recognized standard setting organization's standard. AST device manufacturers also should be permitted at this point to review and validate the new breakpoints for their instruments/systems and provide the data to CDRH for the agency's approval to ensure that AST device algorithms also are kept up-to-date.

- Obviously, FDA should seek out all available opportunities for CDRH and CDER to work together jointly or at least in tandem so that updates to both drug labeling and AST device algorithms can advance as quickly as possible.

- FDA also should consider continuing to use the AIDAC as a forum for expediting the review and acceptance of recommendations from nationally and internationally recognized standard setting organizations, augmenting membership with additional experts as needed, to expedite the adoption of these standards.

Should FDA find the alternatives we have outlined above unworkable then IDSA references our earlier positions articulated at FDA's Part 15 Hearing on antimicrobial resistance in April 2008. That is:

- FDA should create its own scientific board of external experts comprised of infectious diseases clinicians, microbiologists, pharmacologists, and others who understand the clinical impact of changes in the interpretations of the minimal inhibitory concentrations (MIC). Such a board could help the agency update breakpoints and/or review and approve nationally and internationally recognized standard setting organizations' recommendations. To accomplish this, the agency must return to purchasing from private vendors the critically needed susceptibility data used to update breakpoints and require pharmaceutical sponsors (both pioneer and generic) to provide any such additional data as may be needed to update breakpoints quickly; and

- FDA should consider contracting out some of the activities needed to update breakpoints through external organizations, such as CLSI. Infusing some of the agency's patient safety funding into such a contract could help to more quickly update breakpoints.

Turning to the question of updating out-of-date antibacterial drug labels, obviously, FDA's pre-2009 process for updating breakpoint information was not optimal or we would not now be in a position where roughly 70 labels currently are out-of-date. That said:

- IDSA strongly believes FDA should immediately adopt existing CLSI breakpoints for the purpose of updating these out-of-date labels based upon the agency's existing statutory authorities to protect patients' safety or utilize the agency's regulatory discretion, if that is deemed necessary. Answering the question FDA posed in its briefing document, IDSA recommends the agency rely upon these existing standards, even in the setting of incomplete information, as a timely means to update the accumulated out-of-date microbiology information in systemic antibacterial drug product labeling.

From IDSA's perspective, FDA's Office of Antimicrobial Products' staff's time would be much better spent working to remove disincentives from the antibacterial and other anti-infective drug pipelines as well as creating greater regulatory clarity around clinical trial designs for bacterial infections than on evaluating the evidence necessary to update these out-of-date labels. FDA has acknowledged there is problem in the antibacterial drug pipeline. In FDA's March 2004 Critical Path report "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products", the agency reported that "product development in areas crucial to public health goals, such as antibiotics, has slowed significantly during the past decade." However, despite FDA's recent advances, the agency and the federal government in general has dedicated insufficient time and resources to solve the antibacterial resistance and pipeline problems. IDSA hopes that the tide is turning in this critical area and, to enable continued movement in this positive direction, we ask AIDAC members to consider whether a laborious effort to update these out-of-date labels undertaken and led by FDA's staff is the best current use of their time, resources, and energy. In IDSA's opinion, it is not, particularly as CLSI breakpoints may be immediately utilized for this purpose.

Thank you again for the opportunity to speak before you today. IDSA stands ready to work with the FDA and AIDAC in any way that we can to better protect patients against serious and life-threatening infectious diseases.

PhRMA

New Medicines. New Hope.

PhRMA Comments Regarding Breakpoint Updates

Alan Goldhammer, PhD
Vice President for Scientific and Regulatory Affairs

October 26, 2009

Overall considerations

- **Breakpoint updates of approved drugs are merited**
  - Public health is prime consideration

- **Reference Standards Organizations (RSO) are appropriate forums. Considerations:**
  1. Systemic methods for triggering breakpoint update
  2. Professional and defined procedures
  3. Ensure quality of data and analysis

Characteristics of the RSO

Systemic methods for triggering breakpoint update

- **CLSI data guidelines* for initiating a Breakpoint update**
  - Microbiologic, mechanistic, methodological or clinical data
  - Similar to Sept ’09 draft clinical antimicrobial guidance
  - Criteria are subjective
  - “common sense” required for evaluation

- **Systematic approach for initiating breakpoint updates**
  - Date of approval (older are reviewed first)
  - Regular calendar cycles
  - Drug class
  - FDA guidance

***M23 A3 [Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters]**

Characteristics of the RSO

Professional and defined procedures

- **Should model initial FDA review in procedure**
  - Adequate time for review cycles,
  - written Q&A
- **Data integrity and access assured**
- **Review of data by all parties**
- **Flexible due to limitations in data**
- **Procedures needed for review of generic drugs (No Sponsor support)**

Characteristics of the RSO

Professional and defined procedures

PhRMA

Generic Drugs

- **Sponsor support is unlikely**
- **Frequently no recent controlled data sets**
- **Appointment of Rapporteur or Working Group by RSO a possibility**
- **Input and guidance from FDA is very useful**
  - Prioritization of review of generics
  - Reviews ideally similar to Sponsored supported drugs

Characteristics of the RSO

Professional and defined procedures

- **Standards for breakpoint updates is pivotal**
  - Regular review of M23 by main stakeholders:
    - IDSA, Academia, PhRMA, EUCAST, CLSI, and Expert Groups
    - Possible workshop to discuss criteria and weighting
    - CLSI recently updated M23 guidelines following multiple reviews
    - Sept 09 draft guidance is excellent foundation

- **RSO likely to have most recent data and standards**
  - More modern data and testing procedures
  - Default assumption could be RSO breakpoints for dated labels

Characteristics of the RSO

Ensure quality of data and analysis

- **Data included in breakpoint update evaluation**
  - Microbiological
  - PK/PD analysis
  - Clinical
    - Gold standard for Breakpoint determination
    - Case reports and case series to be evaluated with caution
- **No one data source should completely dominate**
- **Quality and quantity of data should be ensured**
  - Potential bias is to report negative results (resistance, failure, etc)
  - Control for severity of illness, salvage versus initial therapy, etc.
- **Ensure review and transparency of data and analysis**

Characteristics of the RSO

Ensure quality of data and analysis

- **Initial FDA Breakpoint: Sponsor supported**
  - All data verified; key clinical data evaluated in blinded manner
  - High quality review: cycles of review, written Q&A.
  - Clear standards, and review procedures for quality process

- **Breakpoint Updates: Post Marketing data (RSO)**
  - Challenges poised by limited or biased data sets.
  - Data rarely verified or evaluated/analyzed in blinded manner.
  - Consequences when updating only one agent within an indication or drug class (encourage or discourage alternative therapies)

Summary

- **Breakpoint updates of approved drugs merited**
- **Use of RSO is appropriate for update reviews**
- **Operating procedures and practices are pivotal**
  1. Systemic methods for triggering breakpoint update
  2. Professional and defined procedures
  3. Ensure quality of data and analysis

Generic Perspective: Labelling Updates for Systemic Antibacterial Drug Products

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Boehringer Ingelheim
Ben Venue Laboratories

Agenda

Boehringer Ingelheim
Ben Venue Laboratories

- Typical Generic Product Labeling
- When the generic becomes the RLD
- Specific Issues and Concerns
- Recommendations for the Agency

Generic Drug Labeling Changes

- Exactly the same as the Reference Listed Drug with few exceptions
- Typically no studies for clinical safety or efficacy are required
- Updated in accordance with the RLD changes
- Timeframes for submission and implementation may differ depending on types of changes
- 21 CFR 314. 94(a)(8)(iv)

When the Generic Becomes the RLD

Boehringer Ingelheim Ben Venue Laboratories

- If the original Reference Listed Drug is discontinued or withdrawn, the first approved generic becomes the RLD

- Other generic firms follow the labeling of the new “RLD”

- Typically very few labeling changes after this point because:
  - there are no post-marketing study commitments or additional clinical information gathered.
  - drug has been marketed for many years and the safety profile is generally established.

Issues and Concerns from the Generic Perspective

Boehringer Ingelheim Ben Venue Laboratories

- Generic firms typically have no unique information gathered from studies or other internal sources

- Expertise with the product history is limited in most cases to Chemistry and Manufacturing Controls, bioequivalence studies and adverse event safety profile

- Must depend on outside literature and information

- Possibility of inconsistency between firms in evaluation and application of standards and information without a defined standard

Submission and Procedural concerns

Boehringer Ingelheim Ben Venue Laboratories

- Definition of the expectation for “periodic” or “regular” updates to susceptibility information

- Prior Approval Supplements have been identified as appropriate path. Timelines for implementation can become prolonged.

- For Office of Generic Drugs, are the supplements intended for the Labeling group or for the Microbiology team?

- Do the supplements for a “generic RLD” require consult with ONDC in order to evaluate past information submitted by the RLD during the approval process?

Recommendations for the Agency

Boehringer Ingelheim Ben Venue Laboratories

Generic Industry is eager to ensure that all labeling is updated with the most recent information and ensures that the products are delivering the expected therapeutic effects.

- Establishment of a standard, as suggested by the Agency, is critical.
  - Internationally recognized
  - Updates should be easily available or published on a routine basis
- Consideration of need for prior approval versus a CBE-30 if the standard is followed.
- For Generic “RLD”, clarify the correct group for review (labeling vs. microbiology)

Recommendations for the Agency

Boehringer Ingelheim Ben Venue Laboratories

With regards to updating the microbiology sections of older products:

- The use of current information from a standard source is imperative for timely updates – in the case of an ANDA that is RLD, it is the only information available
- Reissue letters to NDA/ANDA holders with clear expectations for the submission
  - Comment and feedback on 2008 submission (if applicable)
  - Provide possible sources of reference for information
  - Provide expert contacts within the Agency for questions
  - Required timelines for submission
  - Establish timelines for review within the Agency – task force approach
  - Implementation timeline requirements

Boehringer Ingelheim
Ben Venue Laboratories

Thank you.

Updating Susceptibility Test Information in Systemic Antibacterial Drug Product Labeling

Impact/Analysis to the Antimicrobial Susceptibility Testing Device Manufacturers

October 2009

STMA
SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

STMA Member Companies:

BD

bioMérieux, Inc.

Bio-Rad Laboratories

Hardy Diagnostics

Mast Diagnostics

Oxoid Limited

Siemens Healthcare Diagnostics, Inc.

TREK Diagnostic Systems

SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Updating Susceptibility Test Information – Impact to AST Device Manufacturers

Agenda

- Guidance Documents from FDA – What is Required for AST Device Manufacturers When a Drug Label Changes
- Previously Collected Clinical Trial Data Generally Will Not Suffice for Older Drugs/Devices
- A New Clinical Trial is Only a Small Part of Development Process
  - Antibiotic Qualification Process –MIC
  - Antibiotic Qualification Process – Disk
- Time Considerations
- Organizational and Financial Considerations
- Summary

SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Guidance Documents from FDA

- A change in susceptibility test interpretive criteria for an antibacterial drug results in changes to the label for that drug.

- "If susceptibility test interpretive criteria in the labeling for an AST device do not conform with the updated drug labeling, *AST device manufacturers should update their labeling to conform with the new, publicly available drug labeling within 90 days*." (Guidance for Industry, June 2009)

SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Guidance Documents from FDA

- *Updating breakpoint criteria in an AST device label ordinarily would require submission of a premarket notification* (510(k)) prior to updating labeling. (June 2009)

- To determine device is within scope, manufacturers should reevaluate either
  (a) previously collected clinical trial data applying the revised breakpoint or
  (b) perform a comparative study
  to determine if the drug interpretive criteria change will change the device performance

SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Guidance Documents from FDA

- Comparative study should
  - Follow design described in Class II Special Controls Guidance Document; AST Systems (August 28, 2009, originally issued March 2000)
  - Use a similar group of organisms that provided the original Category Agreement (Breakpoint) or Essential Agreement (+/-1 dilution) results
  - Include a representative number from all groups of organisms that might be affected by modifications to the device

Previously Collected Clinical Trial Data

Generally Will Not Suffice for Older Drugs/Devices When Interpretive Criteria are Changed

- Prior to 2000 AST Guidance Document, AST device data submission followed a different format with different criteria.
- Any submission for a device for an older antimicrobial agent for an older device will
  1. not follow current design
  2. not have data easily available for reprocessing
  3. not include a representative number from all groups of organisms that might be affected by modifications to the device.

Thus necessitating a new clinical trial and new (or redeveloped) product development

SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

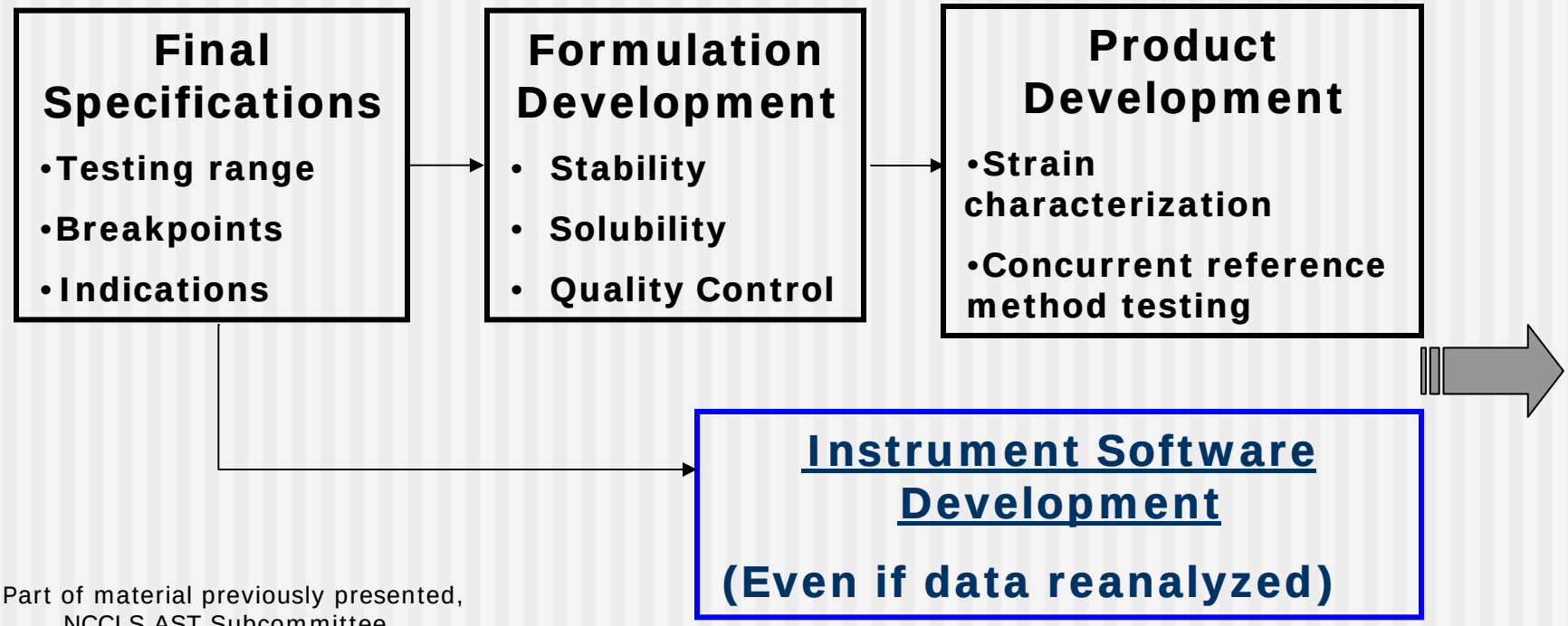
A New Clinical Trial is Only a Small Part

Of the Work Required for AST Devices When Interpretive Criteria are Changed

- New Product Development:
  - New test development for microbiologics and software, required if new interpretive breakpoint is very different than current product configurations.
  - New software releases
  - New product configurations
  - Labeling changes
  - Customer validation

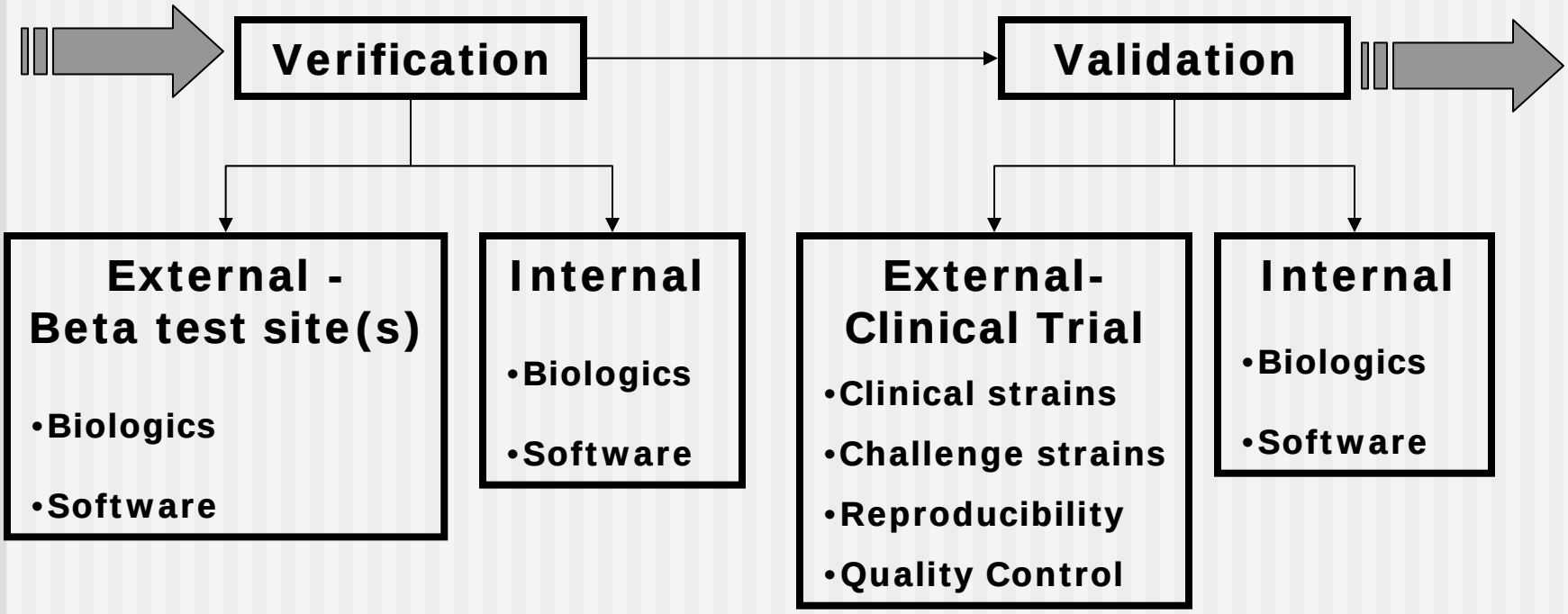
SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Antibiotic Qualification Process for AST Systems -- MIC



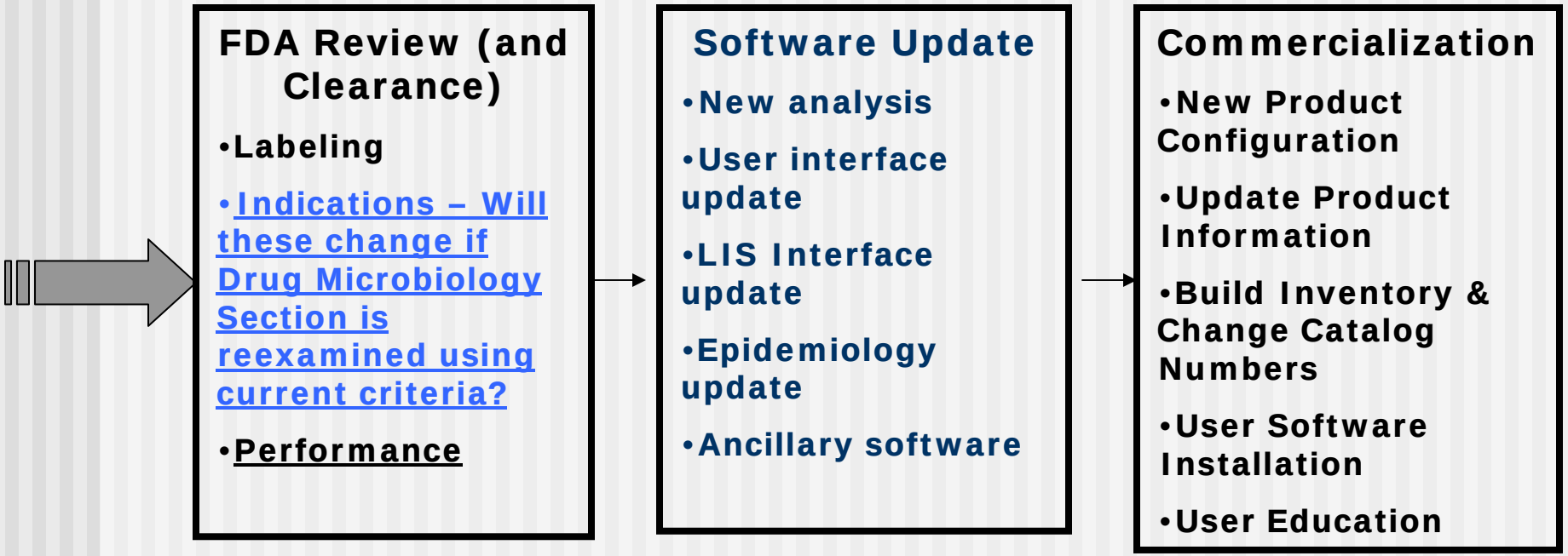
Part of material previously presented,
NCCLS AST Subcommittee,
June 2003, January 2004

Antibiotic Qualification Process for AST Systems -- MIC



SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Antibiotic Qualification Process for AST Systems -- MIC



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Antibiotic Qualification Process -- Disk

The process is simpler; however there are some unanswered questions.

- Does the Guidance Include Disk Diffusion?
- New MIC Interpretive Criteria Generally Require MIC/Disk Correlation Studies. Will FDA also accept new disk breakpoints and/or new QC ranges?
- What process will be followed?

SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Updating Susceptibility Test Information – Impact to AST Device Manufacturers

Time Considerations

- Development Process cannot be completed in 90 days, even if data are reanalyzed and acceptable.
  - Generally 2 year process if no redevelopment, 3 year process for full implementation for Devices.
  - Disk and gradient diffusion are faster, but generally take 6 months for data, clearance, and label changes.
- We would propose that impact to device/test would be analyzed within 90 days of drug label change.
- A more streamlined AST device submission process and acceptance criteria would be beneficial.

SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Updating Susceptibility Test Information – Impact to AST Device Manufacturers

Financial and Organizational Considerations

- Cost to manufacturers could be substantial, including submission costs.
- Budget/ project prioritization
  - Since time and money are constraints, each manufacturer will need to determine priorities. AST development for new compounds may be delayed.
  - Depending on available resources, not all devices may be updated.

SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

Updating Susceptibility Test Information – Impact to AST Device and Disk Manufacturers

Summary: Any interpretive change made to antibacterial drug product labeling affects antimicrobial susceptibility testing devices.

- **Concern:** A 90 day timeline is not adequate for implementation of a single breakpoint change whether only data reanalysis or full product development is required. Multiple breakpoint changes at once further extends timeline. **Recommendation:** Provide time for 2 year process if no redevelopment, 3 year process for full implementation for Devices.
- **Concern:** Total product development, particularly software, costs money and time. Product commercialization changes, including software delivery and product changes, are extensive. **Recommendation:** Continued careful attention to breakpoint changes, only changing those with medical necessity.
- **Concern:** The effect is greater on older drugs and devices; however, newer drugs and devices and disk manufacturers will also be impacted. **Recommendation:** Continued careful attention to breakpoint changes, only changing those with medical necessity.

Antimicrobial Susceptibility Testing Methods and Interpretation: A Public Health Issue

Jean B. Patel, D(ABMM)
Leader, Antimicrobial Resistance Team
Division of Healthcare Quality Promotion

CDC's Mission

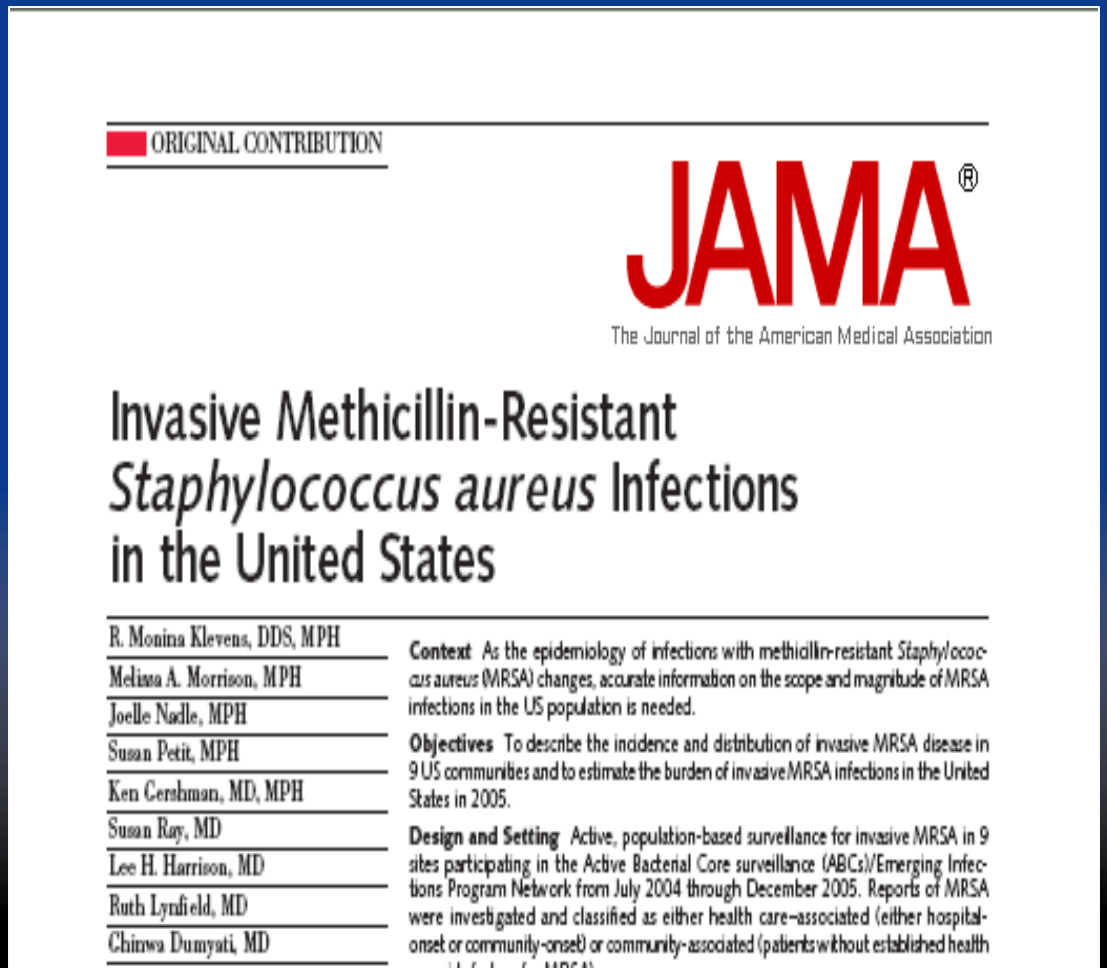
To promote health and quality of life
by preventing and controlling disease, injury, and disability

To detect, prevent, and control antimicrobial resistance

To promote methods for the accurate detection of antimicrobial resistance

Monitoring For Antimicrobial Resistance

Active Bacterial Core Surveillance



ORIGINAL CONTRIBUTION

JAMA®

The Journal of the American Medical Association

Invasive Methicillin-Resistant *Staphylococcus aureus* Infections in the United States

R. Monina Klevens, DDS, MPH
Melissa A. Morrison, MPH
Joelle Nadle, MPH
Susan Petit, MPH
Ken Gershman, MD, MPH
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Context As the epidemiology of infections with methicillin-resistant *Staphylococcus aureus* (MRSA) changes, accurate information on the scope and magnitude of MRSA infections in the US population is needed.

Objectives To describe the incidence and distribution of invasive MRSA disease in 9 US communities and to estimate the burden of invasive MRSA infections in the United States in 2005.

Design and Setting Active, population-based surveillance for invasive MRSA in 9 sites participating in the Active Bacterial Core surveillance (ABCs)/Emerging Infections Program Network from July 2004 through December 2005. Reports of MRSA were investigated and classified as either health care–associated (either hospital-onset or community-onset) or community-associated (patients without established health

Monitoring For Antimicrobial Resistance Trends

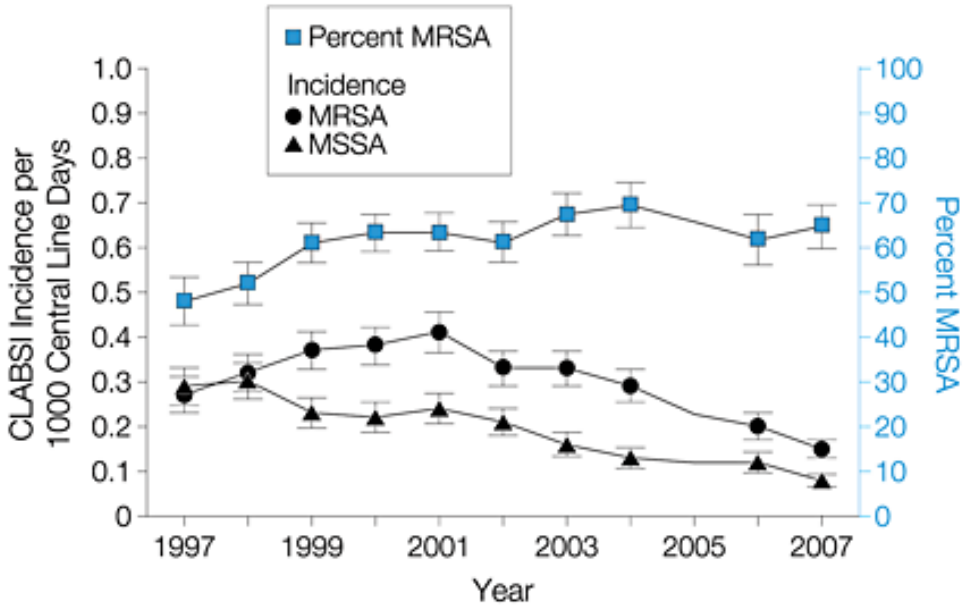
JAMA®

Online article and related content current as of February 17, 2009.

Methicillin-Resistant Staphylococcus aureus Central Line Associated Bloodstream Infections in US Intensive Care Units, 1997-2007

Deron C. Burton; Jonathan R. Edwards; Teresa C. Horan; et al.

JAMA. 2009;301(7):727-736 (doi:10.1001/jama.2009.153)



Antimicrobial Susceptibility Testing (AST) Lab Activities

- Reference susceptibility testing of isolates to confirm new or emerging antimicrobial resistance
- Research to develop and evaluate methods of antimicrobial susceptibility testing

The Results of Our Work

- Recommendations of methods for detecting new or emerging resistance (with a focus on generic methods)
- Recommendations of revised interpretation of susceptibility data for the accurate detection of resistance

Recent Contributions of DHQP Activities

- Carbapenemase detection in Enterobacteriaceae
- Detection of mupirocin resistance in *S. aureus*
- *S. aureus* vancomycin breakpoint changes
- Cefoxitin susceptibility for detection of *mec*A-mediated resistance in *S. aureus*
- Use of vancomycin screen agar for detection of VISA and VRSA
- ESBL detection in Enterobacteriaceae
- Detection of inducible clindamycin resistance in *S. aureus* and β-hemolytic streptococcus
- AST methods for infrequently isolated bacteria
- Interpretation of susceptibility data for *Acinetobacter* spp.

Other CDC Antimicrobial Resistance Activities

- Mycobacteriology
- Nocardia and Aerobic Actinomycetes
- Mycology
- Bacterial Respiratory Pathogens
- Enteric Pathogens
- Viral Diseases

The Unique Role of CDC

- Antimicrobial susceptibility testing expertise
- Capability to validate reference and generic AST methods
- Susceptibility data of new and emerging antimicrobial resistant bacteria
- Unbiased data

Working With a Standards Development Organization

- Increases our potential for a public health impact
  - Participation in a consensus process
  - Facilitates the distribution of information to the appropriate audience

Our Commitment

- CDC will continue monitoring for emerging resistance and conducting AST research
- Data and expertise will be shared with those who have responsibility for setting and revising AST interpretive criteria
  - FDA
  - Standards development organization(s)

Thank You

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